Vasopressor Therapy Using Vasopressin Prior to Crystalloid Resuscitation in Irreversible Hemorrhagic Shock under Isoflurane Anesthesia in Dogs

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(Received 18 August 2006/Accepted 9 January 2007)

ABSTRACT. In the present study, we tested the hypothesis that vasopressin administration prior to crystalloid resuscitation can be used to improve hemodynamic and oxygen delivery functions. Hemorrhagic shock was experimentally induced by maintaining mean arterial pressure at 60 mmHg for 30 min in sixteen healthy dogs weighing from 8 to 10.6 kg. Vasopressin was administered and then volume resuscitation was performed for the 6 dogs of V-C group, while vasopressin was administered at the end of volume resuscitation in the 5 dogs of C-V group. The control group (n=5) was administered 0.4 IU/kg of vasopressin after induction of shock without fluid resuscitation. In all groups, hemodynamic parameters were measured pre- and post-hemorrhage and for 60 min after fluid resuscitation. The dogs in V-C group had substantially increased systolic arterial pressure (SAP) for 60 min and improved pulmonary capillary wedge pressure (PCWP), cardiac output (CO), oxygen delivery, and oxygen consumption indexes compared with C-V and control groups. Diastolic pressure and systemic vascular resistance was significantly lower in the V-C group than those in the C-V and control groups (P<0.05). In the V-C group, there was effective and rapid restoration of the SAP, CO, PCWP, and oxygen delivery parameters after treatment. This study indicates that vasopressin administration before crystalloid resuscitation is a more efficient way of improving hemodynamic and oxygen delivery functions in hemorrhagic shock in dogs.

KEY WORDS: canine, fluid resuscitation, hemorrhagic shock, vasopressin.

**FULL PAPER**

**Internal Medicine**

Vasopressin, an endogenous neurohypophysial hormone, has recently been recognized to be an effective vasopressor that successfully restores circulation when it is unresponsive to fluid resuscitation and catecholamine [13]. Vasopressin differs from other catecholamines because it acts on V1 receptors. Vasopressin preferentially constricts arterioles in extracerebral tissues, with relatively less constriction in renal and coronary blood vessels, and may actually dilate the cerebral and pulmonary vasculature, thereby improving cerebral and pulmonary perfusion [11, 23].

In the case of using a vasopressor in decompensatory hypovolemic shock, fluid therapy is a prerequisite for vasopressor administration. Since vasopressors can reduce blood flow to some tissues, especially the kidney and gut, while transiently increasing cardiac output (CO) in hypovolemic states, it has been indicated that vasopressor therapy should not be instituted unless the circulating blood volume is deemed adequate [10].

In contrast to conventional vasopressor usage in shock patient, Stadlbauer et al. [18] reported that only vasopressin, but not with fluid resuscitation or saline placebo, ensured survival with full recovery in the liver trauma model of uncontrolled hemorrhagic shock in pigs. The present study was designed to test the hypothesis that vasopressin administration prior to crystalloid resuscitation could improve hemodynamic and oxygen delivery functions with minimal complications due to vasoconstriction.

MATERIALS AND METHODS

Sixteen healthy mature mongrel dogs were used in this study. The body weights of the dogs ranged from 8 to 10.6 kg with a mean of 9.3 kg. All dogs used in this study were handled in accordance with the Policy and Regulation for the Care and Use of Laboratory Animals. The dogs were kept in facilities and using procedures that followed the standards established by Seoul National University for Accreditation of Laboratory Animal Care.

Anesthesia was induced immediately by intravenous injection of 10 mg/kg of ketamine HCl (KEIRAN inj., Korea United Pharm, Korea). An endotracheal tube was intubated orally, and anesthesia was maintained with isoflurane (Rhodia Isoflurane, Hana Pharm, Korea) at 1.0–1.2 MAC. To achieve steady state conditions, all dogs were allowed 20 min for stabilization.

The femoral artery was catheterized percutaneously with...
over-the-needle polyethylene catheters (18G, 1.25 inch). The catheter was connected to a calibrated pressure transducer (TranStar Single Monitoring Kit MX9504, Medex Inc., USA) for measurement of systolic (SAP) and diastolic arterial pressures (DAP). A 6-F, 10 cm length, introducer was placed into the right jugular vein by percutaneous puncture, and a 5-F, 75 length, flow-directed Swan-Ganz thermodilution catheter (Safety Wedge™ thermodilution catheter with biotray TD1504NX, Biosensors International, Singapore) was then advanced through the introducer into the jugular vein. The distal end of the catheter was positioned in the pulmonary artery. Correct catheter placement at the pulmonary artery was confirmed by characteristic pulmonary artery and cranial vena cava pressure waveforms on an anesthetic patient monitoring system.

Hemorrhagic shock was induced by exsanguination from the established femoral artery catheter at a spontaneous bleeding rate. Mean arterial pressure (MAP) was maintained at 60 mmHg for 30 min with a total bleeding volume of 30.8 ± 4.6 mL/kg.

The dogs were randomly assigned to a “crystalloid prior to vasopressin (C-V)” group (n=6), a “vasopressin prior to crystalloid (V-C)” group (n=5), and a control group (n=5) (Fig. 1). In the V-C group, 0.4 IU/kg of vasopressin was given bolus via the jugular vein after completion of shock (60 mmHg, 30 min) and 5 min later, a volume of isotonic saline equal to 3 times the volume of bleeding [4] was infused as rapidly as possible (within 5 min). In the C-V group, crystalloid resuscitation was first conducted and immediately after that, vasopressin was given in the same manner as in the V-C group. In the control group, vasopressin was infused after completion of shock but fluid resuscitation was not performed.

The Swan-Ganz catheter was used to measure cardiac output (CO), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), mixed venous hemoglobin saturation (SvO2), arterial hemoglobin saturation (SaO2), mixed venous oxygen tension (PvO2), arterial oxygen tension (PaO2), hemoglobin concentration (Hb), and core body temperature. Cardiac output was determined with an injection of cold isotonic saline (approximately 0°C) through the same catheter at least in triplicate and the mean value was used as data.

Arterial blood was collected into heparinized syringes through the femoral artery catheter and mixed venous blood was collected through the Swan-Ganz catheter. Oxygen delivery parameters, such as PaO2, PvO2, SvO2, SaO2, and Hb, were measured immediately using a blood gas analyzer (OPTI Critical Care Analyzer with Roche E-Ca type OPTI Cassettes, AVL Scientific Corp., U.S.A.). From the above data, cardiac index (CI), systemic vascular resistance index (SVRI), oxygen delivery index (DO2I), and oxygen consumption index (VO2I) were calculated as described previously [2, 12].

Before inducing shock, baseline hemodynamic parameters were measured. Just before induction of shock, oxygen delivery parameters were measured as a baseline. SAP and DAP were measured at 30 min post-hemorrhage, at the completion of crystalloid resuscitation, and at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, and 60 min after vasopressin infusion (C-V and control groups) or crystalloid resuscitation (V-C group). CO and PCWP were determined after vasopressin infusion (C-V and control groups) or crystalloid resuscitation (V-C group) and at 15, 20, 45, and 60 min after infusion (C-V and control groups) or crystalloid resuscitation (V-C group). Oxygen delivery parameters were recorded at 30 and 60 min after vasopressin infusion (C-V and control groups) or crystalloid resuscitation (V-C group).

All values are presented as means ± SD. P<0.05 was considered to be significant in all statistical tests. Data were compared between groups. One-way ANOVA followed by Duncan’s multiple range test (SPSS 12.0K for Windows, SPSS Institute Inc., U.S.A.) was used to compare all pairs of means at the point of same time.

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**Table**

<table>
<thead>
<tr>
<th>Group</th>
<th>Induction of shock</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-C</td>
<td>Maintenance of MAP at 60 mmHg for 30 min</td>
<td>Crystalloid resuscitation for 5 min</td>
</tr>
<tr>
<td>C-V</td>
<td>Maintenance of MAP at 60 mmHg for 30 min</td>
<td>Vasopressin</td>
</tr>
<tr>
<td>Control</td>
<td>Maintenance of MAP at 60 mmHg for 30 min</td>
<td>Vasopressin</td>
</tr>
</tbody>
</table>

Fig. 1. Procedural chart for this experiment.
RESULTS

The changes in CI and PCWP throughout the experimental protocol are shown in Fig. 2. There were larger increases in CI and PCWP after treatment in the V-C group than in the C-V and control groups. The C-V group also showed a significant increase in PCWP and CI compared with the controls (P<0.05).

Vasopressin infusion prior to fluid resuscitation had a significant effect in lowering the systemic vascular resistance (SVR) 15 min and 60 min after treatment compared with the C-V and control groups (Fig. 3). In contrast, the control group showed a remarkably increased SVR compared with the C-V and V-C groups (P<0.05). SAP in the control group remained high until 25 min after administration of vasopressin but abruptly decreased after 30 min (Fig. 4). In contrast, the level of the C-V and V-C groups remained relatively steady for the period from 10 min to 60 min.

Vasopressin administration before crystalloid resuscitation had a significant increasing effect on SAP in the V-C group compared with the C-V and control groups (P<0.05).

The results for HR, CVP, SPAP, and DPAP are shown in Table 1. No significant differences were observed between the C-V and V-C groups after treatment.

DO₂I and VO₂I increased in both the C-V and V-C groups. The V-C group showed a significant increase (P<0.05) in DO₂I compared with the C-V and control groups at 60 min (Fig. 5). VO₂I was increased in the C-V and V-C groups. There were significant increases (P<0.05) in DO₂I in the V-C group compared with the C-V and control groups at 30 and 60 min.

DISCUSSION

Vasopressin prior to crystalloid resuscitation in this study showed better hemodynamic and oxygen delivery effects for controlled hemorrhagic shock in dogs. Although the DAP and SVRI of the V-C group were lower than in the C-V and control groups, the results showed significantly improved CI, SAP, DO₂I, and VO₂I. The V-C group showed a significantly higher SAP and lower DAP compared with the C-V group. This finding may be due to the combined effects of a decrease in heart rate and an increase in stroke volume. Increased stroke volume leads to elevated systemic blood pressure. As heart rate decreases, aortic blood pressure falls to a lower level in the longer periods between heart beats. The exact reason for the increased CO in the V-C group is unknown but can be explained based on the assumption that vasopressin administration cause peripheral vasoconstriction in the state of hypovolemic shock. This is mediated by vasopressin via V₁ receptors located on the vascular endothelium, and this enables vasopressin to maintain vasopressor activity during hypoxia and...
acidosis, which result from prolonged shock state [13]. By virtue of this characteristic, vasopressin can be administered before fluid resuscitation in irreversible hypovolemic shock. Prevasoconstriction might help the increasing preload during crystalloid resuscitation by decreasing the peripheral blood reserve. In contrast to the V-C group, the C-V group was resuscitated with crystalloid in the dilated vasculature before vasopressin administration. In this case, at the time of vasopressin infusion, cardiac output and blood pressure were already rising as a result of fluid resuscitation. Accordingly, vasoconstriction by vasopressin may be counteracted by a baroreceptor-mediated decrease in cardiac output [1], consistent with results of C-V group.

According to a previous report [22], vasopressin was demonstrated to maintain perfusion to the kidneys in experimental hemorrhagic shock and cardiac arrest, in contrast to epinephrine. In addition, Stadlbauer et al. [18] implied that vasopressin may be beneficial when continuous bleeding injuries occur, because it simply shifts blood away from the injury, i.e., from the site of bleeding. Besides the facts described above, exogenous vasopressin administered at subpressor doses induces significant renal vasodilation mediated by nitric oxide [15]. Thus, vasopressin may act as a vasopressor to recover preload more efficiently in redistribution of blood flow than catecholamine with the least complications in terms of vital organs such as the brain, kidney, and lung.

Emerging data from experimental studies [7, 17] show that aggressive fluid resuscitation in hemorrhagic shock could worsen bleeding with uncontrolled hemorrhages and also indicate that there is no advantage over the use of a small volume in the hemorrhagic shock model in dogs. This might be due to increasing blood loss and dilution of the blood resulting in inability to meet oxygen delivery requirements. Furthermore, based on a previous report [5], large volume crystalloid resuscitation causes interstitial edema

Table 1. Heart rate (HR), central venous pressure (CVP), systolic pulmonary arterial pressure (SPAP), and diastolic pulmonary arterial pressure (DPAP) before and after the resuscitation phase in the dogs (mean ± SD)

<table>
<thead>
<tr>
<th>Variable Group</th>
<th>Time after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline*</td>
</tr>
<tr>
<td>HR V-C</td>
<td>135±20</td>
</tr>
<tr>
<td>(beat/min)</td>
<td>143±16</td>
</tr>
<tr>
<td>Control</td>
<td>156±38</td>
</tr>
<tr>
<td>CVP V-C</td>
<td>2.7±2.7</td>
</tr>
<tr>
<td>(mmHg)</td>
<td>2.4±1.9</td>
</tr>
<tr>
<td>Control</td>
<td>1.0±1.7</td>
</tr>
<tr>
<td>SPAP V-C</td>
<td>19.0±2.7</td>
</tr>
<tr>
<td>(mmHg)</td>
<td>17.4±2.2</td>
</tr>
<tr>
<td>Control</td>
<td>18.0±1.7</td>
</tr>
<tr>
<td>DPAP V-C</td>
<td>7.4±5.0</td>
</tr>
<tr>
<td>(mmHg)</td>
<td>9.6±4.8</td>
</tr>
<tr>
<td>Control</td>
<td>4.7±4.9</td>
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</table>

Before the induction of shock. †Completion of shock. a, b) Significant (p<0.05) differences were noted among the different dose groups. Values with different superscript letters are significantly different.
that may actually impair oxygen transport by impairing diffusion of oxygen from the intravascular space to cells. Thus, this may be in agreement with our results, which showed that C-V group had less improvement of oxygen delivery versus oxygen consumption than V-C group, and this mismatch in oxygen consumption versus oxygen delivery ultimately deteriorate the arterial blood pressure [18].

The higher levels of SAP and CO in the V-C group compared with those of C-V group in this study suggest that a smaller fluid volume was adequate to attain the same hemodynamic end-point in the V-C group. This result supports the theory that less fluid administration leads to less fluid shift of vascular fluid into interstitial tissue, improved oxygen delivery, and a faster recovery rate. This is an important advantage because vasopressin can preserve blood flow in important vital organs without adequate body fluids [6, 21], delay multiorgan failure, and help escape the vicious cycle of decompensatory shock [5]. On the other hand, catecholamine requires fluid replacement before administration because of the serious complications of vasoconstriction via \( \alpha_1 \)-receptor and less sensitivity of \( \alpha_1 \)-receptor in hypoxemic environment [19].

Increases in CO and SAP were observed in the V-C group despite a decrease in SVRI. The reasons for the observed changes in these parameters lead to speculations like those below. The decrease in systemic vascular resistance could not be explained in this study and further study in this regard is required.

We speculate, however, that vasopressin may modulate vascular tone and permeability by an unknown mechanism that prevents loss of intravascular fluid to interstitial spaces. Given this, “pooling” in the venules induced by postcapillary vasoconstriction and precapillary dilation in the decompensatory stage of shock [5] may relax such that intravascular hydrostatic pressure is decreased, and this may result in decreased capillary permeability. Clearly, the decrease in fluid shift to extravascular tissue was a striking observation that may have several advantages in managing shock. For example, excessive extracellular fluid accumulation can be avoided, ensuring appropriate extracellular hydration. Bleeding in injured tissue can also be relieved because of decreased intravascular hydrostatic pressure. Finally, early restoration of blood volume leads to better prognosis with a smaller degree of organ failure.

There are several limitations to this study that should be noted. First, blood vasopressin concentration was not measured because this research focused on the hemodynamic effects of vasopressin therapy in cases that can be used in veterinary practice. Measurement of the blood vasopressin concentration is needed to understand the exact action of exogenous vasopressin in hypovolemic shock. Second, organ blood flow was not measured for comparison of the selective distribution of blood flow. Finally, the experimental animals were anesthetized with ketamine and isoflurane during study. Anesthesia may affect cardiac function during experiments, compared with the clinical shock state. The influence of isoflurane on the decrease in blood pressure in dogs is predominantly due to peripheral vasodilation and depression of myocardial function and coronary and systemic vascular resistances [14, 20].

In conclusion, administration of vasopressin prior to fluid resuscitation appears beneficial for rapid restoration of blood flow with a smaller volume of fluid and has the added advantage of preventing harmful fluid interstitial accumulation.

REFERENCES

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